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REGULAR ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Bronchopulmonary dysplasia predicted at birth by artificial intelligence

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Abstract

Aim: To develop a fast bedside test for prediction and early targeted intervention of bronchopulmonary dysplasia (BPD) to improve the outcome.

Methods: In a multicentre study of preterm infants with gestational age 24-31 weeks, clinical data present at birth were combined with spectral data of gastric aspirate samples taken at birth and analysed using artificial intelligence. The study was designed to develop an algorithm to predict development of BPD. The BPD definition used was the consensus definition of the US National Institutes of Health: Requirement of supplemental oxygen for at least 28 days with subsequent assessment at 36 weeks postmenstrual age.

Results: Twenty-six (43%) of the 61 included infants developed BPD. Spectral data analysis of the gastric aspirates identified the most important wave numbers for classification and surfactant treatment, and birth weight and gestational age were the most important predictive clinical data. By combining these data, the resulting algorithm for early diagnosis of BPD had a sensitivity of 88% and a specificity of 91%.

Conclusion: A point-of-care test to predict subsequent development of BPD at birth has been developed using a new software algorithm allowing early targeted intervention of BPD which could improve the outcome.

KEYWORDS

bronchopulmonary dysplasia, chorioamnionitis, respiratory distress syndrome, spectroscopy, surfactant

Abbreviations: BPD, Bronchopulmonary dysplasia; FTIR, Fourier transform infrared spectroscopy; INSURE, Intubation-Surfactant-Extubation; NIH, National Institutes of Health; PLS, Partial least square; PMA, Postmenstrual age; RDS, Respiratory distress syndrome; SVM, Support vector machine.

1 | INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a multifactorial disease in very preterm infants. Intrauterine infections such as chorioamnionitis[1] or silent infections are believed to be important etiological factors. It is a major complication of prematurity, with high mortality and morbidity associated with high treatment costs followed by a continued healthcare burden in childhood and later life.[2]

In our previous study, we developed a machine learning algorithm which measures lung maturity and predicts RDS at birth with high sensitivity and specificity. The algorithm for this lung maturity test rapidly re-creates the lecithin-sphingomyelin ratio measured on gastric aspirate using a routine sample at point of care.[3,4] Unlike RDS, there are no clinically useful predictive tests for BPD available at birth, though many biomarkers are known to be correlated with development of BPD. Therefore, we aimed to develop an artificial intelligence algorithm able to predict BPD soon after birth, which did not require a priori knowledge of specific biomarker identities.

Key Notes

- Bronchopulmonary dysplasia (BPD) is a major cause of mortality and morbidity in premature infants.
- By combining biochemical and clinical data sets and analysing these using artificial intelligence, we have developed an algorithm that can predict BPD at birth.
- Early prediction and targeted intervention of BPD have the potential to improve the outcome.

2 | METHODS

2.1 | Study design and context

The study was a multicentre non-interventional diagnostic cohort study where unique multivariate data sets were created and subsequently analysed by artificial intelligence. The data sets included spectral pattern analysis of gastric aspirate combined with specific clinical data points. Results of this multivariate data analysis were compared with clinical outcomes data specific to BPD.

The patients included in our point-of-care lung maturity test study published in 2019[3,4] were followed for five days after birth to assess the development of RDS. Subsequently, we expanded the scope and extended the duration of the cohort study until 40 weeks of gestational age, enabling us to diagnose development of BPD. This was approved by the local Research Ethical Committees and the study was conducted from July 1, 2019, to December 15, 2019.

2.2 | BPD definition

The Consensus BPD definition from the US National Institutes of Health (NIH) was applied.[5] For infants born at gestational age (GA) <32 weeks, BPD referred to requirement of oxygen support for at least 28 days supplemented with an assessment at 36 weeks postmenstrual age (PMA). Oxygen support day 28 includes all degrees of BPD, and oxygen support at 36 weeks includes the cases with moderate to severe BPD.

The two most used diagnostic criteria for BPD have been Shennan's criteria,[5] based on oxygen need at 36 weeks PMA and the NIH criteria. Compared to Shennan's definition, the NIH consensus identified 80% more infants with BPD and is a better predictor of oxygen requirement at discharge.[5]

2.3 | Participants

Premature infants born between 24 and 31 completed gestational weeks participating in our observational lung maturity test study[3,4] were eligible to participate and were enrolled from three level three and four level two neonatal intensive care units.

Treatment with antenatal steroids, and early nasal continuous positive airway pressure, was performed as previously described.[4] Surfactant was administered in accordance with the current European Consensus Guidelines on the Management of RDS[6] if possible, as early rescue treatment,[7] by INSURE (Intubation-Surfactant-Extubation)[8,9] combined with noninvasive respiratory support.[10]

2.4 | Sampling of gastric aspirate and spectroscopy

Sampling of gastric aspirate at birth was performed as described earlier.[4] Feeding tubes or suction catheters were placed following routine procedures, while establishing nasal continuous positive airway pressure for respiratory stabilisation or intubation for resuscitation. Gastric aspirate was stored at 4-5°C before analysis by mid-infrared Fourier Transform Infrared Spectroscopy (FTIR)[11] using dry transmission.[3]

2.5 | Basic method development principles

A data-driven approach was employed to develop a software algorithm capable of predicting BPD. Clinical data available around the time of birth were combined with FTIR spectral data of gastric aspirate, resulting in the creation of complex multivariate data sets. These data sets were analysed using artificial intelligence and used for the prediction of BPD.

2.6 | Model development

2.6.1 | Partial least square

Partial least square (PLS) is the most widely used method for multivariate data analysis when the covariates are highly co-linear as seen

in spectroscopic data. The PLS algorithm applied in the actual study was developed by Höskuldsson.[12] The score plots, produced by PLS in combination with other classification techniques such as linear discriminant analysis, have in many cases been proven to separate samples for better determination.[13]

2.6.2 | FTIR spectral data

The FTIR[11] spectral analysis range was 900-3400 cm^{-1}. Baseline was corrected using the Savitzky-Golay algorithm,[14] and the 1st derivate was used for spectral data analysis. The Cox-Wilcoxon test was used to further select the most important variables, and 43 wave numbers were selected out of 1200.

2.6.3 | Clinical data

The clinical data points correlated with BPD were determined by the t test for continuous variables and the chi-square test for categorical variables. Two-tailed *P* values < .05 were considered to indicate statistical significance. To identify the data with the highest relevance to the clinical outcome, Lasso regression[15] was applied. Surfactant treatment, birth weight, gestational age, Apgar score at 5 minutes, sex, type of delivery, mechanical ventilation needed on day one, antenatal steroid, maternal diabetes, pre-eclampsia, intrauterine growth retardation and 'clinical chorioamnionitis verified by rupture of the membranes, fever, ± pus in the amniotic fluid' were examined as predictors. Surfactant treatment was found to be most important variable, followed by birth weight and gestational age. The other clinical data did not improve the model and therefore were not used in the calculations. There were no cases with clinical sepsis at birth and no known hereditary dispositions for BPD.

2.6.4 | Support vector machine

Support vector machine (SVM) is an efficient classifier in artificial intelligence developed by Cortes and Vapnik.[16] In classification, SVM separates different types of a data by constructing a hyperplane. A more detailed description of the SVM algorithm can be found in the references.[17,18] To avoid overfitting, and due to the relatively low number of samples, linear kernel was applied along with cross-validation.

2.6.5 | Software

R studio (Microsoft R open)[19] software was used for the analysis. The SVM model was built using the Kernlab package[20] written in R programming language. The validation of the model performance in the training sample was sevenfold cross-validation repeated 500 times. For the cross-validation, the samples were split randomly into seven parts, and one of the parts was used as blind sample. The criterion for selecting the best parameters was the minimisation of classification error. Additionally, the mean sensitivity and specificity of the cross-validation was calculated. The sensitivity was defined as the percentage of the correct prediction of the infants with BPD, and the specificity as the correct prediction of the infants who did not develop BPD.

3 | RESULTS

Of the 72 eligible infants, two died shortly after birth and one on day 21. Four infants were lost to follow-up, and in four cases, the parents refused participation. Thus, 61 very preterm infants were included in the study, as shown in Figure 1. The clinical characteristics of the included infants are presented in Table 1.

Twenty-six (43%) developed BPD, and 35 (57%) did not developed BPD. Ten of the 26 infants with need of oxygen day 28 had moderate-severe BPD with need for supplemental oxygen also at week 36.

Forty (65%) of 61 included infants had either BPD combined with RDS (n = 22), or noBPD and no RDS (n = 18). Four infants with BPD did not have RDS, and 17 infants without BPD had RDS (Table 2).

Infants with BPD had a median birth weight of 850 g and a gestational age of 27.3 weeks, and 20 (77%) were treated with surfactant. Infants without BPD had a median birth weight of 1.356 g and a gestational age of 30.1 weeks, and 7 (20%) were treated with surfactant. Birth weight and gestational age were significantly lower for infants with BPD compared to infants without BPD (*P* < .001), and more infants with BPD than without BPD were treated with surfactant (*P* < .001). Birth weight, gestational age and surfactant

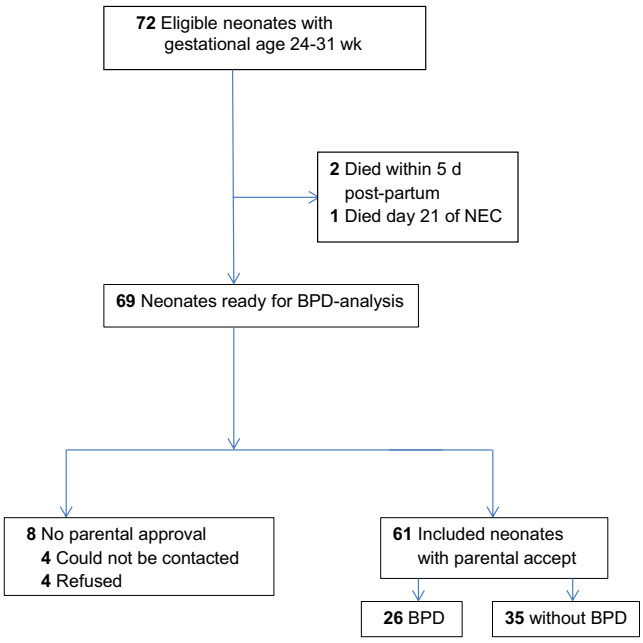

FIGURE 1 Flow chart of inclusion and number of infants with and without BPD. Three infants without BPD died before day 21 and were excluded. BPD indicates bronchopulmonary dysplasia. NEC indicates necrotizing enterocolitis.

TABLE 1 Characteristics of included neonates

Clinical variable	Cohort (n = 61)
Gestational age, wk[a]	28.5 (24.3-31.7)
Birth weight, g[a]	1.014 (525-2.110)
Male[b]	35 (57)
Antenatal steroid[b]	58 (95)
2 doses[b]	48 (83)
Caesarean section[b]	43 (70)
Mechanical ventilation	
Within 5 d post-partum[b]	14 (23)
2 h	8 (13)
Apgar 5 min[a]	9.2 (4-10)
Respiratory distress syndrome[b]	39 (64)
Moderate-severe	28 (46)
Surfactant treatment[b]	27 (44)
Time to surfactant treatment, h[a]	5.8 (0.1-33)

[a]Median (range).
[b]n (%).

treatment are important factors correlated with the development of BPD, and by analysing them using a logistic regression model, the sensitivity and specificity for prediction of BPD were 74% and 82%, respectively. Similar results were obtained by applying SVM resulting in 76% sensitivity and 82% specificity.

As mentioned, the FTIR spectral data analysis of gastric aspirate resulted in identification of the 43 most important wave numbers for classification. A typical gastric aspirate spectrum from an infant born in week 31 is shown in Figure 2. Prediction of BPD from FTIR spectral data of gastric aspirate samples alone is shown in Figure 3A, whereas Figure 3B illustrates how well BPD is predicted when FTIR spectral data and clinical data were combined in the analysis. Predictions were considered accurate in samples where repeated cross-validation outcomes exceeded 50%. Some samples (numbers 01, 40, 41, 42 and 57) which came from infants without BPD, but treated with surfactant early after birth, were difficult to classify from the combined data set of FTIR spectral data and clinical data (Figure 3B). PLS analyses showed that the best prediction of these samples was obtained from analysis of FTIR spectral data only. As seen from Figure 3A, sample numbers 01, 40 and 42 were better predicted using the spectral data alone and prediction of sample 41 was improved from 2% to 45%. Gastric aspirate sample numbers 04, 10, 11 and 35 which came from infants with BPD and no RDS (Figure 3B) were also difficult to classify. Two of these infants, number 10 and 11, could only be classified by the FTIR spectral data (Figure 3A).

TABLE 2 BPD vs RDS

	BPD (n of infants)	no BPD (n of infants)
RDS	22	17
no RDS	4	18

Note: BPD indicates bronchopulmonary dysplasia; RDS indicates respiratory distress syndrome.

By incorporating FTIR spectral data analyses, with the clinical data birth weight, gestational age and surfactant treatment into the linear SVM analysis, the sensitivity increased from 76% to 86% and the specificity from 82% to 85% following cross-validation. Using the parameters selected by cross-validation, the fitting model was finally calculated for the 61 samples revealing a sensitivity and specificity of 88% and 91%, respectively, for prediction of BPD.

One gastric aspirate sample was contaminated with pus. However, it was still possible to measure the sample using FTIR and correctly predict BPD.

4 | DISCUSSION

Early prediction of BPD is of high importance for future development of an effective intervention for the disease. In an overview of current and prospective pharmacologic therapies published by Michael et al,[21] several different strategies were considered such as vitamin A, caffeine, diuretics, surfactant protein D, inositol and early surfactant administration.

Our new algorithm was created to predict BPD soon after birth. Therefore, predictive factors for BPD such as nutrition, long lasting mechanical ventilation, blood gas values and pH after birth and late complications as patent ductus arteriosus and beginning lung fibrosis cannot be used in this algorithm. Rare heriditary diseases[22] may dispose for BPD, but as mentioned in Methods, we do not have such diseases in our population, or at least they are very seldom. Special BPD algorithms may need to be developed in regions with heredity BPD.

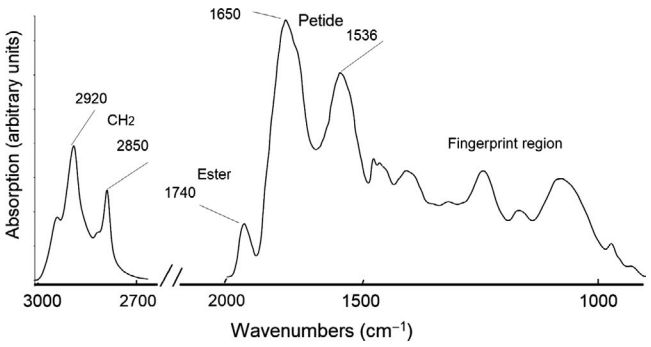

FIGURE 2 Fourier transform infrared spectrum of gastric aspirate from an infant born in week 31. The fingerprint region is the most informative region in the spectrum for analysis of biological material. Each peak denotes a composition of chemical bonds. The spectrum can be further differentiated to obtain underlying signals. To diagnose bronchopulmonary dysplasia, calculations as described in the manuscript are needed. The infant is not included in the actual study. Dipalmitoyl-phosphatidylcholine the most surface-active part of surfactant is expressed in the high peak at 1740 cm^{-1} together with other phospholipids. Therefore, the infant may have mature lungs.

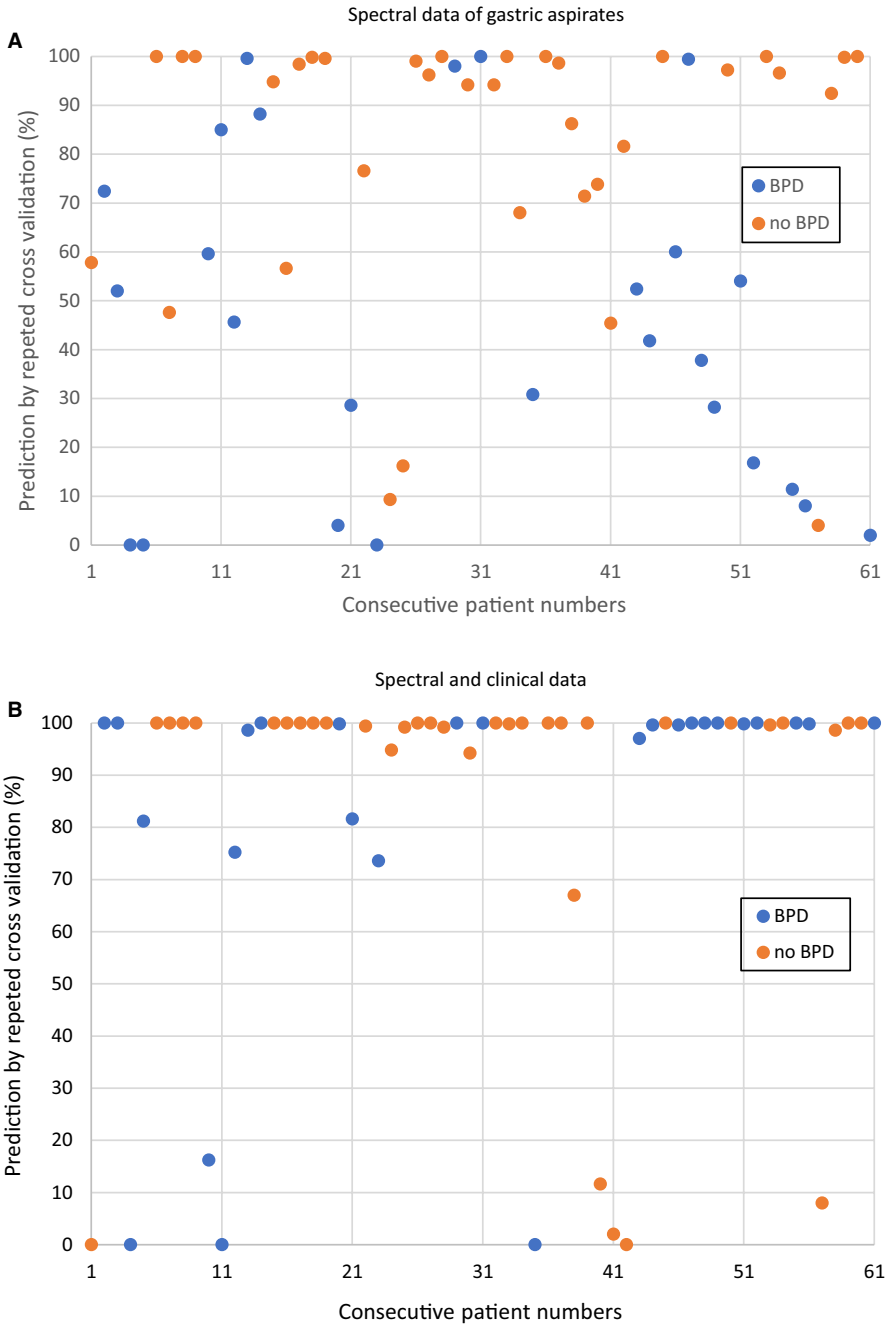

FIGURE 3 Predictions of bronchopulmonary dysplasia (BPD) and no BPD were considered accurate in samples where repeated cross-validation outcomes exceeded 50%. Cross-validation is a method to evaluate how accurately the predictive model will perform in practice. (A) It can be seen that the spectral data predicted the outcome accurately in 42 (69%) of the 61 infants. (B) The combined spectral and clinical data, surfactant treatment, birth weight and gestational age, predicted the outcome accurately in 52 (85%) cases. Infant no 1, 11, 40 and 42 could only be predicted accurately by spectroscopy (A).

Many biomarkers for diagnosis of BPD have been published. Common for these parameters are that they determine BPD longer time after birth compared to our new unique algorithm. Gursoy et al[23] developed a clinical scoring system based on birth weight, gestational age, gender, RDS, hypotension and intraventricular haemorrhage able to predict BPD using the same definition of BPD as this study with high accuracy, but not earlier than 72 hours of life. Many of the existing diagnostic tests include markers linked to infections. This is also the case for sphingomyelin and ceramide metabolites in tracheal fluids, which are elevated in cases with BPD vs no BPD.[24] However, these metabolites need to be measured in special labs and are therefore less useful as clinical diagnostic tests. Also, laborious plasma proteome analyses[25] showed changes in the concentrations related to infections in BPD. Furthermore, neutrophil-to-lymphocyte ratio in blood[26] is an early predictor of BPD. However, the sensitivity at birth was only 52% compared to 61% after 72 hours of life, making it likely that this marker is a better marker for neonatal infections than for prenatal infections. A large review of known biomarkers for BPD prediction is published by Rivera et al.[27]

Our study describes the first algorithm developed by artificial intelligence to predict BPD shortly after birth with high sensitivity and specificity. By using FTIR on gastric aspirate developed mainly in the foetal lungs, we generated a highly detailed digital fingerprint of the foetal lung biochemistry (Figure 2). The FTIR spectral wave lengths and absorption intensity were then analysed by artificial intelligence unveiling unique spectral differences between infants with BPD and no BPD. The best results were generated by combining FTIR spectral data with the clinical data birth weight and gestational age available

at birth and surfactant treatment administered shortly after birth. In a few cases, only spectral analysis was able to discriminate between BPD and no BPD, especially so in less typical cases with BPD and no RDS, and no BPD combined with severe RDS needing surfactant treatment.

It is well known that BPD outcomes for very preterm infants may vary from country to country.[28] This is primarily due to the use of different BPD definitions,[5] but also due to differences in treatment as different modes of respiratory support and postnatal steroid use. All infants in the present study were treated in Danish level three and two neonatal intensive care units that have worked closely together for years using same definitions and treatment criteria as described in the method section. This is illustrated by equal treatment results of BPD outcomes obtained by the Danish treatment groups over time, and the fact that the results are not random. In 2013, in the control group in a randomised trial,[29] 71 of 182 infants (39%) needed supplemental oxygen on day 28 and 27 of 188 (14%) on 36 weeks PMA and in the present study 26 of 61 (43%) had need of supplemental oxygen on day 28 and 10 of 61 (16%) on 36 weeks PMA.

It is important in future studies using our algorithm that the definition of BPD is the same as the definition used in this study, and likewise that the treatment methods are similar, as it otherwise will be necessary to create modified algorithms.

In a large meta-analysis,[30] no significant correlations between RDS and BPD were found. In accordance with their findings, our study also indicates that BPD can develop independently of RDS. It is therefore likely that RDS and BPD are two diseases with different pathophysiology in very preterm infants. Our FTIR measurements of GAS were done using a novel method on a concentrate of lamellar bodies as previously described.[4] We propose that the lamellar bodies concentrate may also contain other BPD biomarkers produced in connection with foeto-placental infections or other conditions. Further studies are needed to investigate and identify the molecules or biomarkers causing the FTIR spectral differences between infants with and without BPD.

We have developed a fully automated digital point-of-care device and machine learning algorithm which can measure lung maturity on gastric aspirate in less than 10 minutes,[4] enabling prediction of RDS and need for early surfactant administration.[3] This point-of-care device can also be used to predict BPD simultaneously with RDS in real time by running a separate AI-derived BPD algorithm on the same gastric aspirate when combined with information of surfactant treatment, birth weight and gestational age. Therefore, in the future, it will be possible at birth to screen high-risk infants for RDS and BPD in the neonatal care unit.

The current study is strengthened by the fact that the participating Danish neonatal centres have consistent treatment methods and have worked closely together for the past 30 years. In addition, it is a strength that the AI-derived algorithm was developed by a multidisciplinary team consisting of clinicians, biochemists, cell biologists, AI-engineers and mathematicians. The limitation of the study is the relatively small numbers of patients included. It is a pilot study, and further development and validation of the predictive BPD algorithm is planned, including data aggregation, blind testing and clinical studies. It is also the hope that other algorithms based on artificial intelligence for early diagnosing of neonatal diseases can be developed by combining clinical data with FTIR mid-infrared spectroscopy.

5 | CONCLUSION

By combining artificial intelligence analyses of mid-infrared lung spectra of gastric aspirates with the clinical data surfactant treatment, birth weight and gestational age, we have developed a fast test to predict development of BPD at birth.

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CONFLICTS OF INTEREST

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REFERENCES

1. Speer CP. Inflammation and bronchopulmonary dysplasia. *Semin Neonatol*. 2003;8:29-38.
2. Mowitz ME, Ayyagari R, Gao W, Zhao J, Mangili A, Sarda SP. Health care burden of bronchopulmonary dysplasia among extremely preterm infants. *Front Pediatr*. 2019;7:510.
3. Schousboe P, Verder H, Jessen TE, et al. Predicting respiratory distress syndrome at birth using fast test based on spectroscopy of gastric aspirates.1. Biochemical part. *Acta Paediatr*. 2020;109:280-284.
4. Heiring C, Verder H, Schousboe P, et al. Predicting respiratory distress syndrome at birth using fast test based on spectroscopy of gastric aspirates. 2. Clinical part. *Acta Paediatr*. 2020;109:285-290.
5. Gomez Pomar E, Concina VA, Samide A, Westgate PM, Bada HS. Bronchopulmonary dysplasia: Comparison between the two most used diagnostic Criteria. *Front Pediatr*. 2018;6:397.
6. Sweet DG, Carnielli V, Greisen G, et al. European consensus guidelines on the management of respiratory distress syndrome - 2016 update. *Neonatology*. 2017;111:107-125.
7. Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. *Cochrane Database Syst Rev*. 2012;11:CD001456.
8. Verder H, Robertson B, Greisen G, et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. *N Engl J Med*. 1994;331(1051–5):9.

9. Blennow M, Jonsson B, Dalström A, Sarman J, Bohlin K, Robertson B. Lung function in premature infants can be improved. Surfactant therapy and CPAP reduce the need of respiratory support. *Läkartidningen*. 1999;31:1571-1576.
10. Isayama T, Iwami H, McDonald S, Beyene J. Association of noninvasive ventilation strategies with mortality and bronchopulmonary dysplasia among preterm infants: a systematic review and meta-analysis. *JAMA*. 2016;316:611-624.
11. De Bruyne S, Speeckaert MM, Delanghe JR. Applications of mid-infrared spectroscopy in the clinical laboratory setting. *Crit Rev Clin Lab Scienc*. 2017;1-20.
12. Höskuldsson A. Common framework for linear regression. *Chemom Intell Lab Syst*. 2015;146:250-262.
13. Barker M, Rayens W. Partial least squares for discrimination. *J Chemom J Chemom Soc*. 2003;17:166-173.
14. Schafer RW. What is a Savitzky-Golay filter. *IEEE Signal Process Mag*. 2011;28:111-117.
15. Tibshirani R. Regression shrinkage and selection via the lasso. *J Royal Stat Soc Series B (methodological)*. 1996;58:267-288.
16. Cortes C, Vapnik V. Support-vector networks. *Mach Learn*. 1995;20:273-297.
17. Schölkopf B, Smola AJ. *Learning with Kernels: Support Vector Machines, Regularization, Optimization, and Beyond*. Cambridge US, London UK: MIT Press, 2001; ISBN-13: 978-0262194754.
18. Burges CJC. A tutorial on support vector machines for pattern recognition. *Data Min Knowl Disc*. 1998;2(2):121-167.
19. R Team Core. *A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing. 2017; 2007.
20. Karatzoglou A, Smola A, Hornik K. kernlab: Kernel-Based Machine Learning Lab. 2018. https://cran.r-project.org/package=kernlab
21. Michael Z, Spyropoulos F, Ghanta S, Christou H. Bronchopulmonary dysplasia: An update of current pharmacologic therapies and new approaches. *Clin Med Insights Pediatr*. 2018;12:1-12.
22. Elhawary NA, Tayeb MT, Abdel-Ghafar S, Rashad M, Alkhotani A-A. TNF-238 polymorphism may predict bronchopulmonary dysplasia among preterm infants in the Egyptian population. *Pediatr Pulmonol*. 2013;48:699-706.
23. Gursoy T, Hayran M, Derin H, Ovali F. A clinical scoring system to predict the development of bronchopulmonary dysplasia. *Am J Perinatol*. 2015;32:659-666.
24. Hendricks-Muñoz KD, Xu J, Voynow JA. Tracheal aspirate VEGF and sphingolipid metabolites in the preterm infant with later development of bronchopulmonary dysplasia. *Pediatr Pulmonol*. 2018;53:1046-1052.
25. Zasada M, Suski M, Szwarc-Duma M, et al. Comparative two time-point proteome analysis of the plasma from preterm infants with and without bronchopulmonary dysplasia. *Ital J Pediatr*. 2019;45:112.
26. Sun Y, Chen C, Zhang X, et al. High neutrophil- to-lymphocyte ratio is an early predictor of bronchopulmonary dysplasia. *Front Pediatr*. 2019;7:464.
27. Rivera L, Siddaiah R, Oji-Mmuo C, Silveyra GR, Silveyra P. Biomarkers for bronchopulmonary dysplasia in the preterm infant. *Front Pediatr*. 2016;4:33.
28. Lui K, Lee SK, Kusuda S, et al. Trends in Outcomes for neonates born very preterm and very low birth weight in11 high-income countries. *J Pediatr*. 2019;215(32–40):e14.
29. Verder H, Ebbesen F, Fenger-Grøn J, et al. Early surfactant guided by lamellar body counts on gastric aspirate in very preterm infants. *Neonatology*. 2013;104:116-122.
30. Villamor-Martinez E, Alvarez-Fuente M, Ghazi AMT, et al. Association of chorioamnionitis with bronchopulmonary dysplasia among preterm infants. A systematic review, meta-analysis and metaregression. *JAMA Network Open*. 2019;2:e1914611.

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